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10/810,486	03/26/2004	Mitsuru Furusawa	690116.401C1	8553

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EXAMINER
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BURKHART, MICHAEL D

ART UNIT	PAPER NUMBER
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1633

MAIL DATE	DELIVERY MODE
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02/08/2008

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

## Office Action Summary

**Application No.**

10/810,486

**Applicant(s)**

FURUSAWA, MITSURU

**Examiner**

Michael D. Burkhart

**Art Unit**

1633

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 11/19/2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

4) ☒ Claim(s) 1, 3, 5, 6, 9, 12-14, 16, 17, 32, 33, 36, 39, 40, 45, 48, 50, 51, 54, 55, 61, 62, 77, 78, 81, 84, 85, 95-146 is/are pending in the application.

4a) Of the above claim(s) 3,5,32,39,40,48,50,77,84,85, 95-125, 127-129 and 146 is/are withdrawn from consideration.

- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,6,9,12-14,16,17,33,36,45,51,54,55,61,62,78,81,126 and 130-145 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

### **DETAILED ACTION**

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/19/2007 has been entered.

### ***Election/Restrictions***

Newly submitted claims 127-129, 134 and 146 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

the additional method step(s) recited in claims 127-129 and 146, i.e. restoring the error-prone frequency of DNA replication, is not found in the elected species of mode of performing the invention, i.e. the method of Example 1 of the instant specification, elected in the response dated 6/5/2006.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 127-129 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

### ***Specification***

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the

following is required: the specification does not provide antecedent basis for the term "a rate of  $10^{-6}$  or greater" as found in claims 6, 51, 126, and 132.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 130-140 and 145 are rejected under 35 U.S.C. 102(b) as being anticipated by Morrison et al (EMBO J., 1993, of record) as evidenced by Burgers (Chromosoma, 1998).

Morrison et al teach yeast strains comprising the *pol3-01* mutation (exonuclease active site) of the *POL3* gene which, *inter alia*, is involved in 3'-5' exonuclease proofreading of gene replication errors (see Introduction and abstract, page 1467). Some of the diploid yeast cell strains created also comprise wild type *POL3*, all strains had wild type *POL2* and *POL1*, and others had a mutation in *PMS1*, also involved in correcting gene replication errors (see Introduction and Table I, page 1469). Thus, the *POL3* gene is considered a DNA polymerase innate to yeast, e.g. claim 133. Burgers teaches that yeast DNA polymerase delta exists as a dimer inherently involved in leading and lagging strand DNA replication (page 218, the abstract, Figs. 1 and 2). Upon growth under selective conditions, the *pol3-01* mutant provided a number of mismatch mutations in the *URA3* gene, some of which involved two changes of the wild-type sequence (Table II). The *pol3-01* mutant had a mutation rate (i.e. provided at least one mismatch) of  $\sim 10^{-6}$  (Table I). The cells acquired a 5-fluoro-orotic acid resistance upon selection

(page 1467, second column, last ¶, and Table II), i.e. a desired hereditary trait. The yeast cells were transformed with a plasmid bearing the mutant *pol3-01* mutant, i.e. an exogenous DNA polymerase, e.g. claims 138, 139 (see Fig. 1, page 1467, second column, second full ¶).

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 6, 9, 12-14, 16, 17, 33, 36, 45, 51, 54, 55, 61, 62, 78, 81, 126, 141, and 142-144 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morrison et al (1993, as above) and Burgers (1998, as above) in view of Tanabe et al (EP 1 054 057, 2000, cited by applicants) and del Cardayre et al (U.S. 6,379, 964, filed 7/15/1999).

The teachings of Morrison et al and Burgers are as above and applied as before. In addition, Morrison et al teach that yeast bearing the *pol3-01* mutation, or mutations in *PMS1*,

exhibit a spontaneous mutator phenotype (page 1467, ¶ linking first and second columns). The *pol3-01* mutant grew substantially as well as wild-type (compare + and - colonies in Fig. 2A). Absent evidence to the contrary, the proofreading function of *POL3* detects errors in the daughter strand of a replication fork, not the parent strand, thus the *pol3-01* mutant would "provide" a difference in the number of errors of one strand (the daughter strand) relative to the parent strand, e.g. as in claim 55.

Neither Morrison et al or Burgers teaches the method step of selecting for a high temperature resistant yeast cell.

Tanabe et al teach the use of mutator strains of cells or organisms to mutagenize genes and select for a given mutant under desired pressure conditions. Certain mutator genes disclosed are several DNA polymerase subunits. See ¶'s [0009]-[0016].

del Cardayre et al teach the selection of cells or organism for the evolution of desired properties (abstract). Yeast strains having a mutator phenotype are disclosed as useful for the methods of del Cardayre et al, with mutations in mismatch repair genes, such as *PMS1*, being one specific example. See column 51, line 57 to column 52, line 48. One desired property disclosed by del Cardayre for selection in yeast cells is thermotolerance, for use in fermentation applications. See column 59, lines 63-65 and column 60, lines 15-22. Certain thermotolerant *S. cerevisiae* strains are proposed as starting points for selection of the desired yeast (column 61, lines 27-45). Method steps for selection of thermotolerant yeast are disclosed, and include selecting for strains able to grow after a heat treatment or growth at elevated temperatures. See column 62, line 41 to column 63, line 18.

The claimed methods of producing a high temperature resistant yeast cell by increasing the error-prone frequency of DNA polymerase delta are essentially taught by Morrison et al. with the exception of the step of selecting and isolating a high temperature resistant yeast cell. The ordinary skilled artisan, seeking a method to develop thermotolerant yeast strains for use in ethanol fermentation, would have been motivated to select the mutator yeast strains of Morrison et al for high temperature resistance because both Tanabe and del Cardayre et al teach mutator strains of yeast to be useful for selecting a desired trait of an organism. del Cardayre et al further suggests that thermotolerance is one such desired trait in yeast. It would have been obvious for the skilled artisan to select the mutator strains of Morrison et al for high temperature resistance because of the known benefit of generating thermotolerant yeast for use in ethanol fermentation as taught by del Cardayre et al. Given the teachings of the cited references and the level of skill of the ordinary skilled artisan at the time of applicants' invention, it must be considered, absent evidence to the contrary, that the ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 6, 9, 12-14, 16, 17, 33, 36, 45, 51, 54, 55, 61, 62, 78, 81, 126, and 130-145 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods using yeast DNA polymerase  $\delta$  with a higher error-prone frequency than wild-type

DNA polymerase  $\delta$  and wherein the polymerase provides mismatched bases at a frequency of  $10^{-6}$  or greater, does not reasonably provide enablement for methods using yeast DNA polymerase  $\delta$  with a lower error-prone frequency than wild-type DNA polymerase  $\delta$ , methods using prokaryotic DNA polymerase  $\delta$ , or methods using polymerases with an error frequency less than  $10^{-6}$ . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. **This rejection is maintained for reasons made of record in the Office Actions dated 8/25/2006, 5/31/2007, and for reasons set forth below.**

***Response to Arguments***

Applicant's arguments filed 11/19/2007 have been fully considered but they are not persuasive. Applicants essentially assert that the claims have been amended in light of the statement by the Examiner bridging pages 3 and 4 of the Office Action.

Presuming this to reference the Final Rejection dated 5/31/2007, the statement in question indicates that the specification is enabling for methods using DNA polymerase  $\delta$  with error-prone frequencies higher than wild-type, and wherein the polymerase provides mismatched bases at a frequency of  $10^{-6}$  or greater. That is, the method must utilize a DNA polymerase  $\delta$  having an error-prone frequency that is high enough (i.e. more frequent than wild-type DNA polymerase  $\delta$ ) to cause the desired action (random mutagenesis of genes), yet still low enough not to be lethal to the yeast cell. However, the instant claims still encompass using DNA polymerase  $\delta$  enzymes with error prone frequencies well outside of the enabled range. Independent claims 1, 45, and 130 do not place any range limitations upon the error-prone



frequency. Furthermore, claims that do (e.g. claims 6, 126) recite that the DNA polymerase provides "at least one" mismatched base pair at a rate of  $10^{-6}$  or greater. The term "at least one" has no upper limit, and thus, at the least, encompasses providing from 1 to 1,000 mismatches per  $10^{-6}$ . Therefore, it is easy to see this limitation does not limit the error-prone frequency of the DNA polymerase  $\delta$  in any meaningful way. For example, a rate of 1,000 mismatches per  $10^{-6}$  base pairs is the same as an error prone frequency of  $10^{-3}$ , which, for reasons of record, is not enabled (cells having DNA polymerase  $\delta$  enzymes with this error-prone frequency are not viable).

### ***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 6, 9, 12-14, 16, 17, 33, 36, 45, 51, 54, 55, 61, 62, 78, 81, 126, and 130-145 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being

unpatentable over claims 1,2, 4, 6-47, 49, 51-76, 78-83, and 86-89 of copending Application No. 10/550,924. **This rejection is maintained for reasons made of record in the Office Action dated 5/31/2007, and for reasons set forth below.**

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

***Response to Arguments***

Applicant's arguments filed 11/19/2007 have been fully considered but they are not persuasive. Applicants essentially assert that the rejection has been noted. Hence, the rejection stands until the claims of either application do not render each other obvious.

***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael D. Burkhardt whose telephone number is (571) 272-2915. The examiner can normally be reached on M-F 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Michael D. Burkhardt  
Examiner  
Art Unit 1633

